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SYNTHESIS AND PROPERTIES OF 4-(3-AMINOTHIENO-[2,3-*b*]PYRIDIN-2-YL)COUMARINS

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Substituted 4-[(3-cyanopyridin-2-yl)thiomethyl]coumarins have been synthesized by the alkylation of 2-mercapto-4,6-dimethylnicotinonitrile with 4-chloromethylcoumarins. Substituted 4-(3-amino-thieno[2,3-b]pyridin-2-yl)coumarins have been obtained by a subsequent intramolecular condensation of the methylene and cyano groups. 6H-Chromeno[4,3-d]thieno[3,2-b:5,4-b']dipyridin-6-ones were isolated as a result of the interaction of these compounds with aldehydes, and their aminomethyl derivatives were synthesized.

Keywords: 4-chloromethylcoumarin, 5*H*-chromeno[3,4-*c*]pyridin-5-one, 6*H*-chromeno[4,3-*d*]thieno-[3,2-*b*:5,4-*b*']dipyridin-6-one, 1,2-dihydropyridine, 4-(thieno[2,3-*b*]pyridin-2-yl)coumarin, aminomethylation.

Natural 4-arylcoumarins (neoflavones) [1-3], as also their synthetic analogs, 4-hetarylcoumarins, display various types of biological activity [4, 5]. In particular, recent investigations of the biological properties of 4-pyridylcoumarins revealed among them compounds with high anticancer [6], anti-inflammatory, analgesic, and antimicrobial [7] activity. In view of these circumstances, the search for synthetic routes towards new pyridine-containing coumarins seemed of interest.

In addition to the main methods of 4-arylcoumarin synthesis [8], the cross-coupling of 4-trifluoromethanesulfonyloxycoumarins and 4-tosyloxycoumarins with (het)arylboronic acids or their pinacol esters [4, 5, 9], and also with hetaryl organometallic compounds [10, 11], is increasingly used at the present time.

4-Chloromethylcoumarin derivatives are convenient intermediates for introduction of a hetaryl substituent into the position 4 of the coumarin system. Recently, using 4-chloromethylcoumarins and the (7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetic acid methyl ester, we improved the synthesis of 4-(2-benzofuryl)coumarins [12] and 4-(2-oxo-2*H*-chromen-3-yl)coumarins [13], respectively.

In the present study, we have used 4-chloromethylcoumarins for the synthesis of 4-(thieno[2,3-*b*]pyridin-2-yl)coumarin derivatives by the alkylation of 2-mercapto-4,6-dimethylnicotinonitrile (see [6]).

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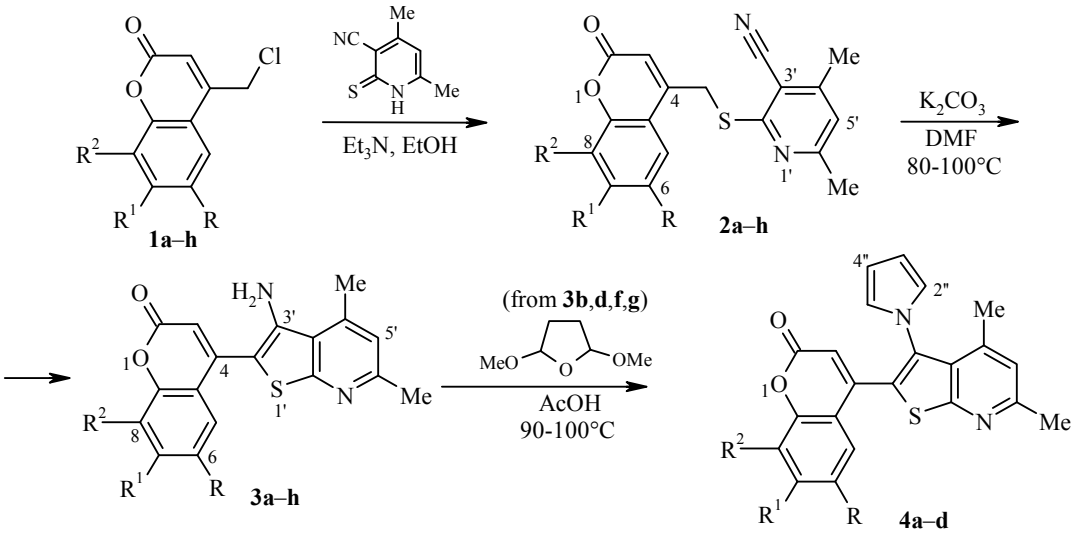


1a–h **2a–h** **3a–h** **4a–d**

1–3 a R = Me, $R^1 = R^2 = H$; **1–3 b**, **4a** R+R^1 = $(CH_2)_3$, R^2 = H; **1–3 c** R = OH, $R^1 = R^2 = H$;
1–3 d, **4b** R = OH, R^1 = Me, R^2 = H; **1–3 e** R = OH, R^1 = Ph, R^2 = H; **1–3 f**, **4c** R = Cl, R^1 = OH, R^2 = H;
1–3 g, **4d** R = Et, R^1 = OH, R^2 = H; **1–3 h** R = H, R^1 = OH, R^2 = Me

Choice of the latter enabled the use of 4-chloromethylcoumarins containing phenolic hydroxyl groups as alkylating agents, since the significant difference in nucleophilicity of the mercapto group and phenolic hydroxyl directed the course of the reaction exclusively to the sulfur atom.

We found that the 4-chloromethylcoumarins **1a-h** interact with 2-mercapto-4,6-dimethylnicotinonitrile in alcohol in the presence of triethylamine at room temperature with the formation of 4-(2-pyridylthio-methyl)coumarins **2a-h** (Tables 1, 2).

The intramolecular cyclization of the methylene and cyano groups in 4-(2-pyridylthiomethyl)coumarins **2a-h** was carried out in DMF under the action of potassium carbonate that led to the formation of substituted 4-(3-aminothieno[2,3-*b*]pyridin-2-yl)coumarins **3a-h**. The synthesized compounds **3a-h** were high-melting yellow substances, sparingly soluble in organic solvents and readily soluble in aqueous solutions of mineral acids and alkali.

The presence of amino groups in compounds **3a-h** was demonstrated by ^{1}H NMR spectroscopy. For instance, a two-proton broadened singlet was observed in the 5.08-5.24 ppm region of the ^{1}H NMR spectra of the synthesized substituted coumarins **3a-h**, which corresponds to the amino group (Table 2).

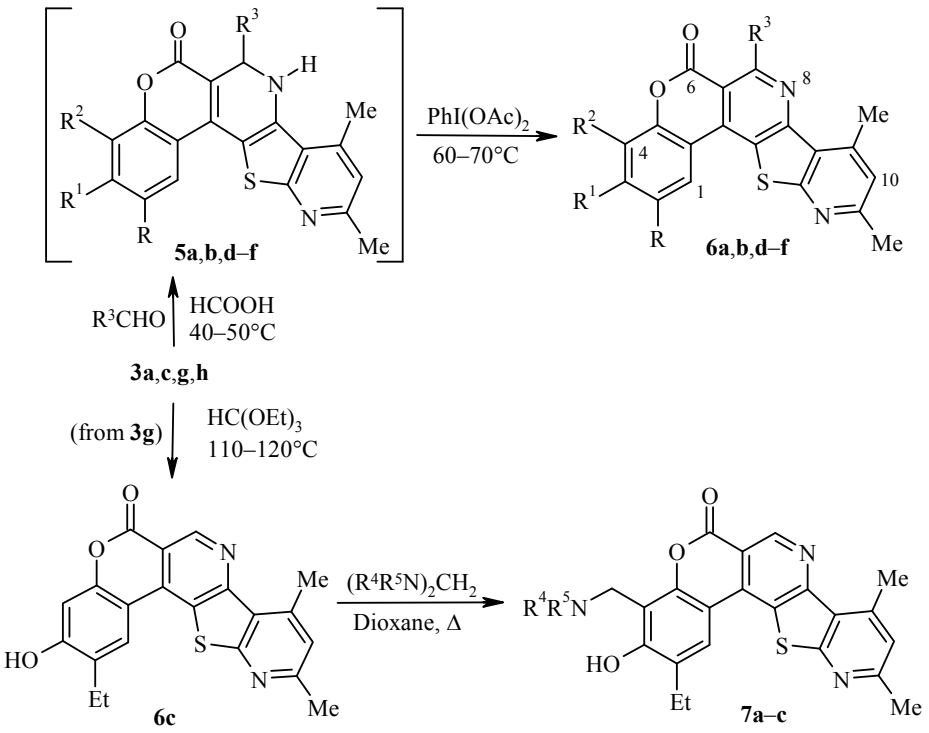
One of the interesting routes for modification of the amino group, in our view, is the construction of a pyrrole ring with the aid of 2,5-dimethoxytetrahydrofuran. We found that brief heating of amines **3b,d,f,g** with this reagent in acetic acid led to the formation of 1-(thieno[2,3-*b*]pyridin-3-yl)pyrroles **4a-d**.

It was shown previously in [7, 12], that 4-(3-aminobenzofuran-2-yl)coumarins are convenient starting materials for the construction of the pyrido[3,4-*c*]coumarin system, which is a structural fragment of alkaloids isolated from *Schumanniophyton problematicum* [14]. At this time various methods for the synthesis of 5*H*-chromeno[3,4-*c*]pyridin-5-one derivatives have been developed (see literature review in [12]).

As it turned out, the interaction of compounds **3a,c,g,h** with aliphatic or aromatic aldehydes in formic acid with subsequent oxidation of the intermediate products **5a,b,d-f** with diacetoxyiodosobenzene enabled the preparation of derivatives **6a,b,d-f** of a new condensed system, 6*H*-chromeno[4,3-*d*]thieno[3,2-*b*:5,4-*b*']dipyridin-6-one. In the case of the synthesis of compound **6c** it proved to be expedient to use triethyl orthoformate [7]. We propose that, as in the case of derivatives of 6*H*-[1]benzofuro[3,2-*b*]chromeno[4,3-*d*]pyridin-6-ones [12], the synthesis of compounds **6a,b,d-f** proceeds through the sequential generation of a Schiff base, its intramolecular cycloaddition with the formation of condensed 1,2-dihydropyridines **5a,b,d-f**, and oxidation of the latter to pyridine derivatives.

TABLE 1. Physicochemical Characteristics of Coumarin Derivatives **1f,g**, **2a-h**, **3a-h**, **4a-d**, **6a-f**, **7a-c**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, %
		C	H	N	S		
1f	$C_{10}H_6Cl_2O_3$	49.17 / 49.01	2.58 / 2.47			271-272	56
1g	$C_{12}H_{11}ClO_3$	60.28 / 60.39	4.53 / 4.65			219-220	72
2a	$C_{19}H_{16}N_2O_2S$	67.65 / 67.84	4.86 / 4.79	8.47 / 8.33	9.41 / 9.53	220-221	80
2b	$C_{21}H_{18}N_2O_2S$	69.67 / 69.59	5.12 / 5.01	7.81 / 7.73	8.93 / 8.85	248-250	77
2c	$C_{18}H_{14}N_2O_3S$	63.76 / 63.89	3.99 / 4.17	8.16 / 8.28	9.56 / 9.48	265-266	81
2d	$C_{19}H_{16}N_2O_3S$	64.85 / 64.76	4.46 / 4.58	7.77 / 7.95	9.22 / 9.10	285-287	79
2e	$C_{24}H_{18}N_2O_3S$	69.47 / 69.55	4.25 / 4.38	6.85 / 6.76	7.82 / 7.74	270-271	75
2f	$C_{18}H_{13}ClN_2O_3S$	58.12 / 57.99	3.64 / 3.51	7.38 / 7.51	8.71 / 8.60	262-264	82
2g	$C_{20}H_{18}N_2O_3S$	65.35 / 65.56	5.07 / 4.95	7.72 / 7.64	8.63 / 8.75	241-242	75
2h	$C_{19}H_{16}N_2O_3S$	64.94 / 64.76	4.47 / 4.58	7.72 / 7.95	9.25 / 9.10	274-275	83
3a	$C_{19}H_{16}N_2O_2S$	67.65 / 67.84	4.89 / 4.79	8.45 / 8.33	9.41 / 9.53	208-210	76
3b	$C_{21}H_{18}N_2O_2S$	69.78 / 69.59	5.13 / 5.01	7.65 / 7.73	8.67 / 8.85	226-228	69
3c	$C_{18}H_{14}N_2O_3S$	63.99 / 63.89	4.28 / 4.17	8.41 / 8.28	9.39 / 9.48	>300	71
3d	$C_{19}H_{16}N_2O_3S$	64.57 / 64.76	4.80 / 4.58	8.14 / 7.95	9.22 / 9.10	>300	75
3e	$C_{24}H_{18}N_2O_3S$	69.38 / 69.55	4.49 / 4.38	6.87 / 6.76	7.67 / 7.74	>300	79
3f	$C_{18}H_{13}ClN_2O_3S$	58.07 / 57.99	3.67 / 3.51	7.29 / 7.51	8.47 / 8.60	186-187	76
3g	$C_{20}H_{18}N_2O_3S$	65.80 / 65.56	4.87 / 4.95	7.75 / 7.64	8.64 / 8.75	259-260	73
3h	$C_{19}H_{16}N_2O_3S$	64.59 / 64.76	4.80 / 4.58	8.14 / 7.95	9.02 / 9.10	>300	75
4a	$C_{25}H_{20}N_2O_2S$	72.92 / 72.79	4.75 / 4.89	6.91 / 6.79	7.85 / 7.77	237-239	46
4b	$C_{23}H_{18}N_2O_3S$	68.46 / 68.64	4.47 / 4.51	6.83 / 6.96	8.05 / 7.97	275-276	58
4c	$C_{22}H_{15}ClN_2O_3S$	62.75 / 62.49	3.73 / 3.58	6.50 / 6.62	7.68 / 7.58	274-275	57
4d	$C_{24}H_{20}N_2O_3S$	69.35 / 69.21	4.90 / 4.84	6.51 / 6.73	7.88 / 7.70	>300	62
6a	$C_{30}H_{26}N_2O_2S$	75.46 / 75.29	5.63 / 5.48	5.73 / 5.85	6.58 / 6.70	301	63
6b	$C_{26}H_{18}N_2O_4S$	68.92 / 68.71	3.87 / 3.99	6.28 / 6.16	6.87 / 7.05	>300	48
6c	$C_{21}H_{16}N_2O_3S$	66.89 / 67.01	4.24 / 4.28	7.65 / 7.44	8.33 / 8.52	>300	65
6d	$C_{22}H_{18}N_2O_3S$	67.81 / 67.67	4.59 / 4.65	7.37 / 7.17	8.44 / 8.21	288-290	38
6e	$C_{28}H_{22}N_2O_4S$	69.82 / 69.69	4.73 / 4.60	5.63 / 5.81	6.54 / 6.64	>300	45
6f	$C_{28}H_{22}N_2O_5S$	67.39 / 67.46	4.59 / 4.45	5.81 / 5.62	6.32 / 6.43	>300	56
7a	$C_{24}H_{23}N_3O_3S$	66.64 / 66.49	5.18 / 5.35	9.79 / 9.69	7.59 / 7.40	>300	76
7b	$C_{26}H_{25}N_3O_4S$	65.92 / 65.67	5.35 / 5.30	8.72 / 8.84	6.82 / 6.74	275-277	58
7c	$C_{28}H_{29}N_3O_3S$	69.14 / 68.97	6.11 / 5.99	8.50 / 8.62	6.68 / 6.58	261-262	61



6 a R = Me, $R^1 = R^2 = H$, R^3 = 4-(*t*-Bu)C_6H_4; **b** R = OH, $R^1 = R^2 = H$, R^3 = 4-$MeOC_6H_4$;
d R = Et, R^1 = OH, $R^2 = H$, R^3 = Me; **e** R = Et, R^1 = OH, $R^2 = H$, R^3 = 4-$MeOC_6H_4$;
f R = H, R^1 = OH, R^2 = Me, R^3 = 3,4-$(MeO)_2C_6H_3$;
7 a $R^4 = R^5$ = Me, **b** $R^4+R^5 = CH_2CH_2OCH_2CH_2$, **c** $R^4+R^5 = CH_2CH_2CH(Me)CH_2CH_2$

The synthesized polycyclic compounds **6a-f** are high-melting crystalline substances, poorly soluble in organic solvents.

On heating compound **6c** with aminals in dioxane, aminomethylation occurs with the formation of Mannich bases **7a-c**, which are readily soluble in organic solvents and in dilute solutions of mineral acids.

Therefore, it has been shown by us that 4-(3-aminohetaryl)coumarins may be convenient starting materials for the synthesis of condensed polycyclic derivatives of 5*H*-chromeno[3,4-*c*]pyridin-5-one. Derivatives of a new heterocyclic system, 6*H*-chromeno[4,3-*d*]thieno[3,2-*b*:5,4-*b'*]dipyridin-6-one, have been synthesized by the interaction of 4-(3-aminothieno[2,3-*b*]pyridin-2-yl)coumarins with aldehydes, followed by intramolecular cyclization and oxidation. Aminomethylation of these compounds under the action of aminals has been studied.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet 380 FT-IR in KBr pellets. The ^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer at 300 MHz, internal standard was TMS. Melting points were determined on a Buchi B-535 instrument. A check on the progress of reactions and the purity of the obtained compounds was carried out by TLC on Merck 60 F254 plates, the eluent was $CHCl_3$–MeOH, 9:1, 19:1.

Compounds **1a-e,h** were synthesized by the procedures of [15-17].

6-Chloro-4-chloromethyl-7-hydroxy-2*H*-chromen-2-one (1f) and 4-Chloromethyl-6-ethyl-7-hydroxy-2*H*-chromen-2-one (1g). A mixture of 4-chloroacetoacetic ester (16.46 g, 0.1 mol) and the 2-substituted resorcinol (0.1 mol) was poured into 73% H_2SO_4 (50 ml) and stirred for 18-24 h at room temperature. The reaction mixture was poured onto ice, the precipitated solid was filtered off, washed with water, and crystallized from MeOH.

TABLE 2. Spectral Characteristics of the Synthesized Compounds **1f,g**, **2a-h**, **3a-h**, **4a-d**, **6a-f**, **7a-c**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)*
1	2	3
1f	3288, 1707, 1614, 1398, 640	5.00 (2H, s, CH_2Cl); 6.49 (1H, s, H-3); 6.94 (1H, s, H-8); 7.86 (1H, s, H-5); 11.51 (1H, s, 7-OH)
1g	3270, 1716, 1618, 1392, 892	1.20 (3H, t, ^3J = 7.4, $CH_2C\underline{H}_3$); 2.62 (2H, q, ^3J = 7.4, $C\underline{H}_2CH_3$); 4.83 (2H, s, CH_2Cl); 6.29 (1H, s, H-3); 6.74 (1H, s, H-8); 7.42 (1H, s, H-5); 10.30 (1H, br. s, 7-OH)
2a	2216, 1716, 1621, 1575, 1543	2.39 (6H, s) and 2.49 (3H, s, 6,4',6'-CH_3); 4.74 (2H, s, CH_2S); 6.59 (1H, s, H-3); 7.15 (1H, s, H-5'); 7.31 (1H, d, ^3J = 8.4, H-8); 7.46 (1H, dd, ^3J = 8.4, ^4J = 1.8, H-7); 7.80 (1H, d, ^4J = 1.8, H-5)
2b	2217, 1708, 1618, 1581, 1556	1.98-2.15 (2H, m, $CH_2C\underline{H}_2CH_2$); 2.39 (3H, s) and 2.49 (3H, s, 4',6'-CH_3); 2.88-3.00 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 4.72 (2H, s, CH_2S); 6.50 (1H, s, H-3); 7.14 (1H, s, H-5'); 7.25 (1H, s, H-8); 7.80 (1H, s, H-5)
2c	3185, 2216, 1677, 1417	2.40 (3H, s) and 2.50 (3H, s, 4',6'-CH_3); 4.70 (2H, s, CH_2S); 6.58 (1H, s, H-3); 7.08 (1H, dd, ^3J = 8.9, ^4J = 1.7, H-7); 7.16 (1H, s, H-5'); 7.24 (1H, d, ^4J = 1.7, H-5); 7.28 (1H, d, ^3J = 8.9, H-8); 9.82 (1H, s, OH)
2d	3187, 2217, 1678, 1579, 1416	2.23 (3H, s, 7-CH_3); 2.40 (3H, s) and 2.50 (3H, s, 4',6'-CH_3); 4.64 (2H, s, CH_2S); 6.50 (1H, s, H-3); 7.15 (1H, s), 7.16 (1H, s) and 7.19 (1H, s, H-5,5',8); 9.72 (1H, s, OH)
2e	3193, 2220, 1678, 1579, 1411	2.41 (3H, s) and 2.51 (3H, s, 4',6'-CH_3); 4.70 (2H, s, CH_2S); 6.60 (1H, s, H-3); 7.17 (1H, s, H-5'); 7.35 (2H, s, H-5,8); 7.36-7.47 (3H, m) and 7.62-7.68 (2H, m, H Ph); 10.00 (1H, s, OH)
2f	3245, 2222, 1716, 1599, 1585	2.39 (3H, s) and 2.49 (3H, s, 4',6'-CH_3); 4.70 (2H, s, CH_2S); 6.43 (1H, s, H-3); 6.91 (1H, s, H-8); 7.16 (1H, s, H-5'); 8.06 (1H, s, H-5); 11.47 (1H, s, OH)
2g	3238, 2218, 1679, 1605, 1384	1.12 (3H, t, ^3J = 7.5, $CH_2C\underline{H}_3$); 2.40 (3H, s) and 2.50 (3H, s, 4',6'-CH_3); 2.56 (2H, q, ^3J = 7.5, $C\underline{H}_2CH_3$); 4.72 (2H, s, CH_2S); 6.34 (1H, s, H-3); 6.77 (1H, s, H-8); 7.14 (1H, s, H-5'); 7.61 (1H, s, H-5); 10.61 (1H, s, OH)
2h	3178, 2218, 1678, 1605, 1573	2.16 (3H, s, 8-CH_3); 2.39 (3H, s) and 2.49 (3H, s, 4',6'-CH_3); 4.67 (2H, s, CH_2S); 6.34 (1H, s, H-3); 6.89 (1H, d, ^3J = 8.8, H-6); 7.13 (1H, s, H-5'); 7.63 (1H, d, ^3J = 8.8, H-5); 10.44 (1H, s, OH)
3a	3413, 1712, 1699, 1560	2.34 (3H, s, 6-CH_3); 2.53 (3H, s) and 2.77 (3H, s, 4',6'-CH_3); 5.21 (2H, s, NH_2); 6.48 (1H, s, H-3); 7.08 (1H, s, H-5'); 7.38 (1H, d, ^3J = 8.6, H-8); 7.47 (1H, dd, ^3J = 8.6, ^4J = 1.8, H-7); 7.51 (1H, d, ^4J = 1.8, H-5)
3b	3411, 1709, 1621, 1548	1.99-2.11 (2H, m, $CH_2C\underline{H}_2CH_2$); 2.52 (3H, s) and 2.77 (3H, s, 4',6'-CH_3); 2.82-3.00 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 5.16 (2H, s, NH_2); 6.40 (1H, s, H-3); 7.07 (1H, s, H-5'); 7.34 (1H, s, H-8); 7.50 (1H, s, H-5)
3c	3463, 1673, 1562, 1446, 1230	2.53 (3H, s) and 2.77 (3H, s, 4',6'-CH_3); 5.20 (2H, s, NH_2); 6.46 (1H, s, H-3); 6.98-7.13 (3H, m, H-5,5',7); 7.32 (1H, d, ^3J = 8.4, H-8); 9.65 (1H, s, OH)
3d	3442, 1659, 1618, 1444, 1411	2.23 (3H, s, 7-CH_3); 2.53 (3H, s) and 2.77 (3H, s, 4',6'-CH_3); 5.17 (2H, s, NH_2); 6.39 (1H, s, H-3); 7.07 (1H, s, H-5'); 7.12 (1H, s, H-5); 7.24 (1H, s, H-8); 9.60 (1H, s, 6-OH)
3e	3398, 1710, 1562, 1413, 1286	2.53 (3H, s) and 2.79 (3H, s, 4',6'-CH_3); 5.24 (2H, s, NH_2); 6.49 (1H, s, H-3); 7.08 (1H, s, H-5'); 7.30 (1H, s, H-5); 7.34-7.49 (3H, m, H Ph); 7.62-7.68 (2H, m, H Ph); 7.40 (1H, s, H-8); 9.83 (1H, s, OH)
3f	3465, 1701, 1608, 1448, 1365	2.52 (3H, s) and 2.79 (3H, s, 4',6'-CH_3); 5.21 (2H, s, NH_2); 6.40 (1H, s, H-3); 6.85 (1H, s, H-8); 7.08 (1H, s, H-5'); 7.35 (1H, s, H-5); 11.52 (1H, s, OH)
3g	3482, 2915, 1697, 1614, 1369	1.10 (3H, t, ^3J = 7.5, $CH_2C\underline{H}_3$); 2.53 (3H, s) and 2.77 (3H, s, 4',6'-CH_3); 2.57 (2H, q, ^3J = 7.5, $C\underline{H}_2CH_3$); 5.17 (2H, s, NH_2); 6.21 (1H, s, H-3); 6.82 (1H, s, H-8); 7.08 (1H, s, H-5'); 7.46 (1H, s, H-5); 10.66 (1H, s, OH)

TABLE 2 (continued)

1	2	3
3h	3411, 1706, 1605, 1562, 1369	2.21 (3H, s, 8-CH_3); 2.52 (3H, s) and 2.76 (3H, s, 4',6'-CH_3); 5.08 (2H, s, NH_2); 6.21 (1H, s, H-3); 6.84 (1H, d, ^3J = 8.8, H-6); 7.06 (1H, s, H-5'); 7.40 (1H, d, ^3J = 8.8, H-5); 10.52 (1H, s, OH)
4a	1708, 1618, 1548, 1421	1.92 (3H, s, 4'-CH_3); 1.98-2.10 (2H, m, $CH_2C\underline{H}_2CH_2$); 2.59 (3H, s, 6'-CH_3); 2.80-2.99 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 6.07-6.13 (2H, m, H-2",5"); 6.53 (1H, s, H-3); 6.90-6.96 (2H, m, H-3",4"); 7.22 (1H, s, H-5'); 7.26 (1H, s, H-8); 7.43 (1H, s, H-5)
4b	1685, 1560, 1415, 1211	1.91 (3H, s, 4'-CH_3); 2.20 (3H, s, 7-CH_3); 2.60 (3H, s, 6'-CH_3); 6.12-6.16 (2H, m, H-2",5"); 6.53 (1H, s, H-3); 6.88-6.92 (2H, m, H-3",4"); 6.96 (1H, s, H-5); 7.20 (1H, s, H-5'); 7.25 (1H, s, H-8); 9.60 (1H, s, OH)
4c	3434, 1726, 1600, 1357	1.92 (3H, s, 4'-CH_3); 2.60 (3H, s, 6'-CH_3); 6.09-6.13 (2H, m, H-2",5"); 6.44 (1H, s, H-3); 6.91 (1H, s, H-8); 6.96-7.00 (2H, m, H-3",4"); 7.23 (1H, s, H-5'); 7.58 (1H, s, H-5); 11.58 (1H, s, OH)
4d	3446, 1728, 1618, 1357, 1272	1.06 (3H, t, ^3J = 7.4, $CH_2C\underline{H}_3$); 1.92 (3H, s, 4'-CH_3); 2.53 (2H, q, ^3J = 7.4, $C\underline{H}_2CH_3$); 2.59 (3H, s, 6'-CH_3); 6.09-6.12 (2H, m, H-2",5"); 6.32 (1H, s, H-3); 6.75 (1H, s, H-8); 6.94-6.97 (2H, m, H-3",4"); 7.23 (1H, s, H-5'); 7.31 (1H, s, H-5); 10.71 (1H, s, OH)
6a	2960, 1738, 1589, 1537, 1062	1.38 (9H, s, $C(CH_3)_3$); 2.48 (3H, s, 2-CH_3); 2.59 (3H, s) and 2.87 (3H, s, 9,11-CH_3); 7.27 (1H, s, H-10); 7.36-7.42 (1H, m, H-4); 7.48 (2H, d, ^3J = 8.4, H-3',5'); 7.53-7.59 (1H, m, H-3); 7.64 (2H, d, ^3J = 8.4, H-2',6'); 8.07-8.12 (1H, m, H-1)
6b	3437, 1736, 1540, 1510, 1250	2.45 (3H, s) and 2.69 (3H, s, 9,11-CH_3); 3.86 (3H, s, OCH_3); 6.98 (2H, d, ^3J = 8.1, H-3',5'); 6.99 (1H, s, H-10); 7.08-7.13 (1H, m, H-3); 7.26-7.30 (1H, m, H-4); 7.56-7.58 (1H, m, H-1); 7.61 (2H, d, ^3J = 8.1, H-2',6'); 10.03 (1H, s, H-2)
6c	3353, 1666, 1556, 1418	1.00 (3H, t, ^3J = 7.6, $CH_2C\underline{H}_3$); 2.24 (3H, s) and 2.37 (3H, s, 9,11-CH_3); 2.52 (2H, q, ^3J = 7.6, $C\underline{H}_2CH_3$); 6.32 (1H, s, H-4); 6.87 (1H, s, H-1); 6.92 (1H, s, H-10); 8.56 (1H, s, H-7); 10.58 (1H, s, OH)
6d	3430, 1733, 1693, 1616, 1504	1.11 (3H, t, ^3J = 7.6, $CH_2C\underline{H}_3$); 2.42 (3H, s), 2.49 (3H, s) and 2.59 (3H, s, 7,9,11-CH_3); 2.52 (2H, q, ^3J = 7.6, $C\underline{H}_2CH_3$); 6.46 (1H, s, H-4); 6.94 (1H, s, H-10); 7.31 (1H, s, H-1); 10.50 (1H, s, OH)
6e	3431, 1720, 1616, 1500, 1249	1.30 (3H, t, ^3J = 7.6, $CH_2C\underline{H}_3$); 2.59 (3H, s) and 2.88 (3H, s, 9,11-CH_3); 2.68 (2H, q, ^3J = 7.6, $C\underline{H}_2CH_3$); 3.87 (3H, s, OCH_3); 6.77 (1H, s, H-4); 7.00 (2H, d, ^3J = 8.1, H-3',5'); 7.21 (1H, s, H-10); 7.58 (2H, d, ^3J = 8.1, H-2',6'); 8.03 (1H, s, H-1); 10.56 (1H, s, OH)
6f	3423, 1742, 1612, 1529, 1496, 1257	1.99 (3H, s, 4-CH_3); 2.50 (3H, s) and 2.62 (3H, s, 9,11-CH_3); 3.73 (3H, s, 3'-OCH_3); 3.87 (3H, s, 4'-OCH_3); 6.70-6.79 (1H, m, H-2); 6.94-7.02 (2H, m, H-2',5'); 7.11-7.18 (1H, m, H-6'); 7.30 (1H, s, H-10); 7.55-7.57 (1H, m, H-1); 10.58 (1H, s, H-3)
7a	3446, 2964, 1730, 1604, 1560	1.38 (3H, t, ^3J = 7.6, $CH_2C\underline{H}_3$); 2.50 (6H, s, $N(CH_3)_2$); 2.71 (3H, s) and 3.08 (3H, s, 9,11-CH_3); 2.77 (2H, q, ^3J = 7.6, $C\underline{H}_2CH_3$); 4.13 (2H, s, CH_2N); 7.15 (1H, s, H-10); 8.17 (1H, s, H-1); 9.52 (1H, s, H-7)
7b	3437, 2962, 1738, 1605, 1562	1.36 (3H, t, ^3J = 7.6, $CH_2C\underline{H}_3$); 2.57-2.87 (9H, m) and 3.06 (3H, s, $N(CH_2)_2$, $C\underline{H}_2CH_3$, 9,11-CH_3); 3.68-3.97 (4H, m, $(CH_2)_2O$); 4.16 (2H, s, CH_2N); 7.13 (1H, s, H-10); 8.08 (1H, s, H-1); 9.43 (1H, s, H-7)
7c	3431, 2927, 1726, 1601, 1558	0.97-1.05 (3H, m, 4'-CH_3); 1.39-1.57 (6H, m) and 1.74-1.84 (2H, m, $CH_2C\underline{H}_3$, 4'-CH, 3',5'-CH_2); 2.29-2.45 (2H, m) and 3.10-3.15 (2H, m, $N(CH_2)_2$); 2.72 (3H, m) and 3.09 (3H, s, 9,11-CH_3); 2.77 (2H, q, ^3J = 7.6, $C\underline{H}_2CH_3$); 4.16 (2H, s, CH_2N); 7.16 (1H, s, H-10); 8.17 (1H, s, H-1); 9.52 (1H, s, H-7)

*The ^1H NMR spectra of compounds **1f,g**, **2a-h**, **3a-h**, **4a-d**, and **6a-f** were recorded in DMSO-d_6, and of compounds **7a-c** in $CDCl_3$.

4,6-Dimethyl-2-{[(2-oxo-2*H*-chromen-4-yl)methyl]thio}nicotinonitriles 2a-h (General Method). A mixture of 3-cyano-2-mercapto-2,4-dimethylpyridine (1.64 g, 10 mmol) and Et_3N (1.69 ml, 12 mmol) in warm EtOH (25-30 ml) was added to a solution of 4-chloromethylcoumarin **1a-h** (10 mmol) in the minimum volume of EtOH at 40-50°C. The reaction mixture was stirred at room temperature for 18-24 h, diluted with 5 volumes of water, the precipitated solid was filtered off, and the residue was crystallized from EtOH.

4-(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)-2*H*-chromen-2-ones 3a-h (General Method). Anhydrous K_2CO_3 (0.69 g, 5 mmol) was added to a mixture of coumarin **2a-h** (10 mmol) in anhydrous DMF (20 ml) at 60-80°C. The reaction mixture was stirred for 6-8 h at 80-100°C, filtered while hot, the solvent was evaporated, and the residue was crystallized from a 1:1 mixture of DMF–MeOH.

4-(4,6-Dimethyl-3-(1*H*-pyrrol-1-yl)thieno[2,3-*b*]pyridin-2-yl)-2*H*-chromen-2-ones 4a-d (General Method). A mixture of amine **3b**,**d**,**f**,**g** (2 mmol), 2,5-dimethoxytetrahydrofuran (0.52 ml, 4 mmol), and glacial acetic acid (20 ml) was heated at 90-100°C for 10-15 min, cooled, and the solvent was distilled off in vacuum. The residue was crystallized from MeOH.

9,11-Dimethyl-6*H*-chromeno[4,3-*d*]thieno[3,2-*b*:5,4-*b*']dipyridin-6-ones 6a,b,d-f (General Method). A solution of 4-(3-aminothieno[2,3-*b*]pyridin-2-yl)coumarin **3a**,**c**,**g**,**h** (1.5 mmol) and aldehyde (2.0 mmol) in HCOOH (20 ml) was heated at 40-50°C for 0.5-1 h. Then diacetoxyiodosobenzene (0.8 g, 2.5 mmol) was added to the red solution, and the mixture was stirred at 60-70°C for 2-3 h. The light-yellow colored mixture was diluted with cold water, the precipitated solid was filtered off, dried, and crystallized from DMF (compounds **6a**,**b**,**e**,**f**) or dioxane (compound **6c**).

2-Ethyl-3-hydroxy-9,11-dimethyl-6*H*-chromeno[4,3-*d*]thieno[3,2-*b*:5,4-*b*']dipyridin-6-one (6c). A mixture of compound **3g** (1.1 g, 3 mmol) and triethyl orthoformate (2 ml, 12 mmol) was heated at 110-120°C for 6 h, cooled, diluted with MeOH (5 ml), the precipitated solid was filtered off and crystallized from a 1:2 mixture of DMF–MeOH.

4-Aminomethyl-2-ethyl-3-hydroxy-9,11-dimethyl-6H-chromeno[4,3-*d*]thieno[3,2-*b*:5.4-*b*']dipyridin-6-ones 7a-c (General Method). The corresponding aminal (1.2 mmol) was added to a hot solution of compound **6c** (0.38 g, 1.0 mmol) in dioxane (10 ml), the mixture was refluxed for 3-5 h, then cooled. The solvent was evaporated in vacuum, and the residue was crystallized from EtOH.

REFERENCES

1. J. B. Harborne and H. Baxter, *Handbook of Natural Flavonoids*, Vol. 1-2, John Wiley & Sons, New York (1999).
2. R. D. H. Murray, *Nat. Prod. Rep.*, **12**, 477 (1995).
3. J. B. Harborne (editor), *The Flavonoids: Advances in Research since 1986*, Chapman and Hall, London (1994), p. 239.
4. O. G. Ganina, E. Daras, V. Bourgarel-Rey, V. Peyrot, A. N. Andresyuk, J.-P. Finet, A. Yu. Fedorov, I. P. Beletskaya, and S. Combes, *Bioorg. Med. Chem.*, **16**, 8806 (2008).
5. C. Bailly, C. Bal, P. Barbier, S. Combes, J.-P. Finet, M.-P. Hildebrand, V. Peyrot, and N. Wattez, *J. Med. Chem.*, **46**, 5437 (2003).
6. K. Harada, H. Kubo, Y. Tomigahara, K. Nishioka, J. Takahashi, M. Momose, S. Inoue, and A. Kojima, *Bioorg. Med. Chem. Lett.*, **20**, 272 (2010).
7. I. A. Khan, M. V. Kulkarni, M. Gopal, M. S. Shahabuddin, and C.-M Sun, *Bioorg. Med. Chem. Lett.*, **15**, 3584 (2005).
8. M. M. Garazd, Ya. L. Garazd, and V. P. Khilya, *Khim. Prirod. Soedin.*, 199 (2004).
9. G. M. Boland, D. M. X. Donnelly, J.-P. Finet, and M. D. Rea, *J. Chem. Soc., Perkin Trans. 1*, 2591 (1996).
10. J. Wu and Z. Yang, *J. Org. Chem.*, **66**, 7875 (2001).

11. L. Schio, F. Chartreaux, and M. Klich, *Tetrahedron Lett.*, **41**, 1543 (2000).
12. M. S. Frasinyuk, S. V. Gorelov, S. P. Bondarenko, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 1568 (2009). [*Chem. Heterocycl. Compd.*, **45**, 1261 (2009).]
13. E. Schlittler and U. Spitaler, *Tetrahedron Lett.*, **19**, 2911 (1978).
14. Y. Fall, L. Santana, M. Teijeira, and E. Uriarte, *Heterocycles*, **41**, 647 (1995).
15. M. S. Frasinyuk, S. P. Bondarenko, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 361 (2009). [*Chem. Heterocycl. Compd.*, **45**, 290 (2009)].
16. M. S. Frasinyuk, V. I. Vinogradova, S. P. Bondarenko, and V. P. Khilya, *Khim. Prirod. Soedin.*, 485 (2007).